REMARKS

Claims 1-11 were pending in the present application. By this Amendment, Applicants have amended claims 1 and 10 to incorporate subject matter from dependent claims 5 and 11, respectively. Applicants have canceled claims 4, 5, 8, and 11 without prejudice to the right to present the canceled subject matter in a future continuing application. This Amendment does not introduce any new matter and thus its entry is respectfully requested. Upon entry of the present Amendment, claims 1-3, 6-7, and 9-10 will be pending and under examination.

July 13, 2006 Office Action

Claim Rejections Under 35 U.S.C. § 112

In the July 13, 2006 Office Action, claims 1-4, 6-8, and 10-11 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action stated that claims 1-3, 6-7, and 10 are drawn to methods of inhibiting tumor growth with a combination of 5-fluorouracil and a "methylol transfer agent." According to the Office Action, the specification provides two examples of methylol transfer agents: taurolidine and taurultam (page 2, paragraph 10), but does not describe the structural features of other methylol transfer agents. Thus, according to the opinion expressed in the Office Action, Applicants have not provided the means for a skilled artisan to visualize or recognize what compounds, aside from taurolidine and taurultam, are included in the phrase "methylol transfer agents."

The Office Action also stated that claims 4, 8, and 11 are drawn to methods of inhibiting tumor growth with a combination of 5-fluorouracil and taurolidine, taurultam, or "a biologically

active derivative thereof." According to the position stated in the Office Action, the specification does not describe the structural features of biologically active derivatives of taurolidine and taurultam. The Office Action asserted that the skilled artisan is provided with no guidance on how to synthesize a biologically active derivative of taurolidine or taurultam, and no guidance on what structural features the Applicants consider to be essential for a compound to be a "biologically active derivative" of taurolidine or taurultam. According to the position stated in the Office Action, the Applicants have provided no means for the skilled artisan to visualize, recognize or synthesize any such "biologically active derivatives" of taurolidine or taurultam.

In response, without conceding the correctness of the position stated in the Office Action, but to expedite allowance of the application, Applicants have amended claims 1 and 10 to incorporate subject matter from claims 5 and 11, respectively, and have canceled claims 4, 5, 8, and 11 without prejudice. The claims, as amended, recite that the methylol transfer agent is "taurolidine, taurultam, or a mixture thereof," and do not contain the language that forms the basis of the written description rejections. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U.S.C. §103(a)

Claims 1-11 were rejected under 35 U.S.C. §103 as allegedly being obvious in view of art previously made of record in the case. Specifically, claims 1-11 were rejected as being unpatentable over Carter, in view of WO 92/00743 for the reasons previously set forth in the Office Action mailed December 15, 2005. According to the present Office Action, Carter discloses that 5-FU is useful to treat the instantly recited cancers. The Office Action

acknowledges that Carter does not disclose a method of using taurolidine or taurultam to treat cancer. The Office Action asserts, however, that WO 92/00743 (pages 1-3) does disclose a method of using taurolidine and taurultam to treat cancer and that it contemplates (at page 3, first paragraph) co-administering taurolidine and/or taurultam with "other agents known to be involved in tumor metabolism" or "cytotoxic agents." The position stated in the previous Office Action was:

> "'[I]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition and use it in a method for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art.' *In re Kerkhoven* 105 USPQ 1069."

"Therefore," the Office Action continued, "in the absence of a showing of unexpected results, it would be obvious to one of ordinary skill to combine 5-FU and taurolidine or taurultam to yield the instant composition and use it in a method to treat cancer, since each is individually taught in the prior art to be useful to treat cancer."

Claims 1-11 also were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Carter, in view of US 6,303,596 for the reasons set forth in the previous Office Action. The Office Action reiterated the rationale set forth above, again asserting that Carter discloses that 5-FU is useful to treat the instantly recited cancers, but does not disclose a method of using taurolidine or taurultam to treat cancer. However, according to the Office Action, U.S. Pat. No. 6,303,596 (abstract and claims) does disclose a method of using taurolidine and taurultam to treat cancer. The present Office Action concludes that it would have been prima facie obvious to combine 5-FU and taurolidine or taurultam to treat cancer. According to the Office Action, taurolidine and 5-FU are individually known in the art as agents for treating cancers, whose

efficacy when administered alone is well established for the treatment of a large number of neoplasia and metastasis. The Office Action stated that it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The Office Action asserted that it is not necessary in such fact situations that the motivation come explicitly from the references themselves in establishing obviousness. According to the Office Action, the natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. The Office Action stated that Applicants have presented no evidence (e.g., unexpected results) to rebut this natural presumption.

In responding to the Applicants' previous arguments, the Office Action stated that Applicants' assertions of the unexpected synergistic effect of the claimed combination are not sufficient to overcome the obviousness rejection without further detail. Specifically, the Office Action stated that

> [f]or example, to demonstrate unexpected results commensurate in scope with the claims, applicants need to show that a combination of 5-FU and taurolidine results in greater inhibition of cell proliferation than would be expected if the effects of each agent individually were added together. An additive effect would be expected and not evidence of surprising results.

In response, Applicants respectfully traverse the rejections under 35 U.S.C. §103(a). As noted previously, the present specification describes an unexpected synergistic effect of the combination of 5-FU and a methylol transfer agent in the treatment of cancer. In that regard, the specification provides an example showing a significant decrease in proliferation of colo-rectal tumor cells following treatment by taurolidine (a metholyl transfer agent) and 5-FU, and indicating that there was an increase in LDH release, which correlated with inhibited tumor

proliferation. Moreover, taurolidine was found to augment (i.e., enhance) the effects of given doses of 5-FU. Furthermore, as previously noted, U.S. Pat. No. 6,479,481, to which the present application claims priority as a continuation-in-part, discloses the use of Taurolidine and/or Taurultam with antineoplastic agents for the treatment of cancer, and the concomitant reduction of side effects upon such use. (See especially, Example 2). These benefits include, for example, "avoid[ing] or reduc[ing] side effects such as nausea, vomiting, diarrhea, etc., induced by use of neoplastic medicaments." The '481 patent also teaches synergistic effects of such combinations, stating that "[t]he dosage of these antineoplastic medicaments can be reduced by up to half or more and still increase the overall response rate (disease stabilization rate) by synergistic effects," and that the reduction is substantial enough to avoid or reduce radiotherapy (and thus its strong side effects) in many cases. (Column 9, lines 19-24). Moreover, in addition to the specific disclosure that the Office Action has acknowledged, i.e., use of a combination of Taurolidine and/or Taurultam with 5-FU after surgical resection of glioblastoma, there is also a Table shown at column 10 which indicates that 5-FU is particularly suitable for combination with Taurolidine/taurultam to achieve the synergistic results described in the Example. The specification therefore teaches that the claimed combination provides an unexpected synergistic effect that results in significant, identifiable increases in anti-cancer effectiveness and significant, identifiable reductions in the common side effects typically induced by neoplastic agents.

Applicants now attach hereto a Rule 132 Declaration executed by named co-inventor H. Paul Redmond, presenting the further details of unexpected results that the Office Action is seeking. In the Declaration, Dr. Redmond describes and shows graphical data demonstrating that taurolidine enhances the anti-neoplastic effects of 5-FU. In particular, the combination of

taurolidine and 5-FU results in greater efficacy in reducing proliferation of colorectal tumor cells than the additive effect that would be expected upon their combination. A benefit of this combination therapy is the ability to use a reduced amount of 5-FU, which then allows for a reduction in the frequency and/or severity of the adverse effects of 5-FU, without diminished efficacy. Applicants believe that the unexpected synergistic effect of the claimed combination, as described and demonstrated in the attached Rule 132 Declaration, would not have been expected based on the teachings of the art of record and thus the claims, as amended herein, are not rendered obvious over any combination of the art cited in the Office Action. Applicants therefore respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

Double Patenting rejection

Claims 1-11 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,479,481, in view of the disclosure in '481. Although the conflicting claims are not identical, the Office Action asserted that they are not patentably distinct from each other because the '481 patent discloses a method of treating tumors using the methylol transfer agents taurolidine, taurultam or a mixture thereof, and teaches that it may be combined with 5-FU to treat glioblastoma (column 9, lines 13-43).

In response, Applicants reiterate that they would be willing to file a Terminal Disclaimer should any conflicting claims be found allowable.

In view of the above remarks, claim amendments, and accompanying evidence of unexpected and surprising results, Applicants believe that the rejections set forth in the July 13, 2006 Office Action have been fully overcome and that the present claims fully satisfy the patent statutes. Applicants therefore believe that the application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

January 11, 2007 By: _____

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Attachment: Rule 132 Declaration of H. Paul Redmond

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